Mini Review

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Neuromodulation for functional restoration: recent advances and future perspectives

Abstract

This mini-review assessed recent studies of spinal cord stimulation and neuromuscular stimulation in spinal cord injury in order to provide an overview of recent advances in neuromodulation for functional restoration. Possible mechanisms of such motor recovery were analyzed, ways to improve neuromodulation for functional restoration were discussed, and future perspectives were outlined in this paper. Recent advancements in neuromodulation such as spinal cord stimulation and neuromuscular stimulation in spinal cord injury have made it possible for patients with incurable complete paralysis to recover motor function. The progress of recent neuromodulation studies in spinal cord injury have demonstrated the value and potential of neuromodulation in functional restoration. The effectiveness and precision of neuromodulation can be further improved by techniques such as closed-loop control, optogenetics, multi-modal stimulation and neuroimmune modulation, while its adverse effects can be reduced (e.g., by optimizing parameters) or minimized (e.g., by using non-invasive techniques). This has opened up new possibilities to use neuromodulation for other incurable neurological diseases such as Parkinson's disease and multiple sclerosis. Neuromodulation has great potential for restoring lost functions and reestablishing physiological homeostasis. To reach its full potential, much learning, research and development is needed. As neuromodulation technology advances, it is foreseeable that neuromodulation will achieve significant clinical effectiveness in functional restoration in the near future, which will bring cure to patients with incurable neurological diseases and relieve them from suffering.

Keywords: neuromodulation, spinal electrical stimulation, deep brain stimulation, optogenetics, functional restoration

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Introduction

There have been case reports in the literature that alternative medicine such as acupuncture and massage enabled motor recovery in patients with paralysis (due to stroke, brain or spinal cord injury, Bell's palsy, multiple sclerosis and Parkinson's disease).[1-3] For example, acupuncture could significantly improve patients' motor function and even set patients free from wheelchairs, which is a miracle.[1] However, the overall clinical effectiveness of such alternative medicine is empirical, elusive and heterogeneous, and the mechanism is unknown.[2,3] Recent neuromodulation studies in patients with complete paralysis have shown surprising results. A "neural bypass" system—a brain-computer-interface (BCI) controlled neuromuscular electrical stimulation system and motor training enabled a patient with quadriplegia from cervical spinal cord injury (SCI) to use his hand and wrist for daily living motion tasks.[4] In addition, spinal cord stimulation (epidural electrical stimulation) and task-specific rehabilitation training restored leg movements of standing and stepping (on a treadmill) in 5 patients with paralysis (including 4 patients with sensorimotor complete paralysis).[5-8] Moreover, non-invasive transcutaneous electrical stimulation combined with pharmacological intervention and rehabilitation training enabled another 5 patients with motor complete paralysis to recover stepping-like movements.[9] These significant motor improvement results are miracles in a sense that these studies have demonstrated phenomenal and promising motor recovery through neuromodulation in patients with paralysis, which challenges our current knowledge and understanding of chronic, complete paralysis after injury in the central nervous system (CNS) and how neuromodulation re-activates motor function that seems to be permanently lost due to injury.[6,8-10]

Why are the miracles possible?

Patients paralyzed by severe spinal cord injury usually have very little chance of motor recovery after half a year from the injury, but why motor recovery was achieved in these patients with sensorimotor complete paralysis years following injury? Why the lost motor function was regained in paraplegic patients even after the critical recovery time window was closed? The mechanism of such motor recovery is unfolding.[5,6,9,10] Recovery of voluntary motor control is possible only when sufficient functional reconnections in the CNS networks take place. Neurons in spinal lesions (that can not conduct action potentials due to injury) can be activated by neuromodulation (which, in some sense, is like what a pacemaker does to a dysfunctional heart -- to activate it and regulate its beats) and become electrical competent. Constant electrical and/or pharmacological neuro-stimulation and repetitive task-specific sensorimotor rehabilitation training promote activity-based plasticity of spinal and residual supraspinal networks through neurogenesis and neuroregeneration, which re-establishes functional connectivity in the CNS networks, facilitates functional reorganization of neural connectivity and enhances motor recovery.[10] An induced timing-dependent current can reduce action potential (or change activation threshold) of a neuron, modify its excitability, improve axon growth, enhance synaptic plasticity, and increase connections between neurons, which promotes neurogenesis, neuroregeneration and neurorepair.[11] Studies have shown that neurostimulation at subthreshold levels of neural-and-spinal network excitability is important to recover voluntary motor control of lower limbs and restore urinating function in patients with spinal cord injury.[10,12] However, it is unclear how these neural networks are modulated at molecular, cellular and systematic levels, and further research is needed to reveal the detailed mechanisms of neuromodulation in motor recovery in patients with sensorimotor complete paralysis years following injury. For comprehensive reviews on neuromodulation for spinal cord injury, see.[11-16] In summary, repetitive spinal cord stimulation and rehabilitation training activate neural circuits and promote plasticity.[5,6,10] Epidural stimulation enables patients with paralysis to process sensory inputs to regain motor control of paralysed muscles.[6] Further, the combination of non-invasive electrical spinal cord stimulation, pharmacology and training increases excitability of the sensorimotor networks (even below the motor threshold), promotes functional reorganization of the CNS circuitry connectivity and facilitates motor recovery.[9]

How to improve neuromodulation?

The results of recent neuromodulation studies in SCI are very encouraging,[4-9] but the following questions remain: How to improve the clinical effectiveness of neuromodulation such as deep brain stimulation (DBS) and spinal electrical stimulation (SES)? How to optimize neuromodulation and rehabilitation training to achieve the best functional reorganization for full motor recovery? Since complete paralysis is usually incurable, encouraging results such as those in recent neuromodulation studies in SCI have opened up new possibilities to use neuromodulation for other incurable neurological diseases such as multiple sclerosis (MS), Parkinson's disease (PD), and cerebral palsy. How to enhance the accuracy and clinical efficacy of neuromodulation to reach its full potential to treat such incurable symptoms/diseases?

The answer may lie in the following three perspectives.

First, personalized and precise neuromodulation

Much learning and research is needed to understand the patterns and mechanisms of normal and abnormal neural rhythms of electromagnetic "waves" in the nervous system in healthy subjects and patients in order to restore physiological homeostasis in patients.

1. Personalized neuromodulation

Each person's normal neural rhythms of electromagnetic "waves" in the neural system (i.e., neurons conduct action potentials to pass or process information from one to another in a neural network) are unique, which is like multi-dimensional (electrical, magnetic, chemical, neuro-immoral, etc.) music (e.g., symphony) in harmony in physiological state. However, in a disease state (e.g., after brain or spinal cord injury, or stroke), the harmonic music-like normal rhythms in the nervous system are disrupted, which leads to abnormal rhythms like silenced broken music with on-and-off off-key sound (or noise) due to the disconnected neural networks.

The aim of neuromodulation is to normalize the electromagnetic "waves" in the nervous system by instilling energy (electronic, magnetic, ultrasound, light, etc.) into the neural system to reactivate, reconnect and reorganize it and by re-establishing physiological homeostasis to recover lost functions. Towards this end, much learning and research of the normal and abnormal patterns of neural rhythms in the nervous system is needed. For example, in Parkinson's disease (PD), abnormal synchronized neural activity in the basal ganglia network has been discovered in patients with PD (17), which has become the basis for desynchronization modulation therapy such as coordinated reset neuromodulation. In epilepsy and seizure disorders, spike synchronization has been observed in EEG data and the tonic/clonic ictal patterns of hyper-synchronized neuronal firing in the seizure onset zone have been detected (18). In addition, the knowledge of how peripheral nerves regulate the state of the central nervous system (CNS) helps to treat a number of disorders and dysfunctions using peripheral nerve stimulation such as Vagus nerve stimulation (VNS). The better we learn the patterns and mechanisms of normal and abnormal neural rhythms in various nervous systems, the better we will be able to mimic normal neural rhythms in pathological nervous systems for functional restoration and symptom relief.

2. Precise neuromodulation

(1) Closed-loop system improves modulation precision by learning from feedbacks of changes in neural function and automatically adjusting stimulation parameters of on-demand neuromodulation (in real-time) towards an optimal (or normal) function. For example, BCI-based closed-loop "neural bypass" system and motor training has restored a hand and wrist function in a paralyzed patient years after spinal cord injury.[4] The neural signals can be recorded using modalities such as fMRI (functional MRI), EEG (electroencephalography), intracranial EEG and spinal epidural electrodes, which provides feedbacks of changes in neural function in the BCI-based closed-loop systems. Further, closed-loop control has been applied to optogenetics,[19] which is significantly more accurate than closed-loop electrical stimulation.[20] In addition, closed-loop VNS promotes post-injury neural plasticity in the motor system and has been used to treat upper limb paralysis in pre-clinical models.[21] However, currently, there are only a few closed-loop clinical neuromodulation devices available, including a spinal cord stimulator for pain relief (Saluda Medical's Evoke) and a neuromodulation device for epilepsy treatment (NeuroPace RNS). Further research and development are needed to make more closed-loop clinical neuromodulation devices available.

(2) Electrical stimulation may be improved and optimized by using optimal radiofrequency to reduce adverse effects,[22,23] and using new technologies such as coordinated reset (CR) neuromodulation to treat diseases that are caused by abnormally synchronized neuronal activities. CR neuromodulation desynchronizes PD-related pathological neuronal synchrony, reshapes synaptic connectivity and shifts the basal ganglia network into a stable desynchronized state, which leads to significant improvement in motor function in PD (24). In addition, CR neuromodulation therapy has been applied to epilepsy[25] for seizure control, to tinnitus for tinnitus symptom relief (26), and potentially to essential tremor for tremor control.[27]

(3) The limitation of lack-of-spatial-specificity in current electrical stimulation approach (DBS, SES, VNS, etc.) may be overcome by using new techniques such as optogenetics to guide these systems to improve specificity. Preclinical studies have indicated that optogenetics allows cell-specific stimulation.[20,28,29] For example, when optogenetics stimulated a specific group of neurons (enriched with parvalbumin) in the external globus pallidus (GPe), mobility was restored in Parkinsonian mice, but when optogenetics stimulated neurons in the GPe in general (not-cell-specific), mobility was not restored.[29] In addition, optogenetics cell-specific stimulation stopped locomotor sensitization to cocaine and synaptic plasticity that evoked by cocaine in rodents, but DBS failed (because electrical stimulation was not specific to cells) and activated two opposing signaling cascades simultaneously (28). However, DBS can be improved by administrating a dopamine receptor antagonist (that blocked the opposing signaling) which abolished behavioral sensitization to cocaine.[28] These preclinical studies have demonstrated that cell-

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specific stimulation has great potential in functional restoration[28,29] and optogenetics-inspired electrical stimulation can achieve similar therapeutic effect as that of optogenetics.[28]

Second, multi-modal neuromodulation

Recent neuromodulation studies on motor recovery in SCI have clearly indicated that electrical stimulation was not performed alone, but in the presence of repetitive task-specific rehabilitation training.[4-9] In addition, the BCI ("neural bypass"), electrical stimulation and motor training together enabled recovery of hand and wrist movement in the paralyzed patient,[4] and the combination of non-invasive electrical and pharmacological stimulation and motor training resulted in voluntary motor control of stepping-like movements in another 5 patients.[9] Moreover, two interleaved epidural electrical stimulation (EES) programs enabled independent stepping in a patient with sensorimotor complete paralysis due to spinal cord injury.[8] These studies have shown that the therapeutic effect of electrical stimulation alone is limited, but the combination of electrical stimulation, pharmacological stimulation and motor training strongly promotes activity-dependent plasticity and improves therapeutic effect. Further, neuromodulation and cognitive training have enhanced cognition.[30] Neurons that fire together usually survive and thrive together. Multimodal neuro-stimulation simultaneously stimulates neurons in multiple ways in the nervous system, which facilities re-establishment of activity-dependent connectivity, reactivation of activity-related neural networks and reorganization of these networks for functional restoration. For a comprehensive review on multimodal neuromodulation, see.[11]

Third, neuroimmune modulation

Neuroinflammation plays a detrimental role in a number of neuropsychiatric disorders such as stroke, brain or spinal cord injury, PD, MS, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and autism. Effective neuroinflammation control in these disorders may slow down disease progression and reduce symptoms. Recent studies on neuronal-immune interaction have found that the nervous system regulates the immune system.[31,32] and recent clinical trials have proved that VNS successfully modulated inflammation, significantly inhibited the production of pro-inflammatory cytokines and ameliorated inflammatory diseases such as rheumatoid arthritis.[33,34] These studies open up new possibilities to treat inflammatory or inflammation-related diseases through neuromodulation (especially promising to those currently incurable symptoms/diseases such as AD, PD, ALS, MS, autism, and stroke-or-CNS-injury-caused paralysis). However, further research is needed to improve our understanding of the neural mechanisms regulating the immune system in these neuropsychiatric disorders and explore how to modulate neuroinflammation to restore physiological homeostasis in such disorders.

Future directions

The rapid advancements of optogenetic technology (especially the technical breakthroughs of viral vector in recent years) open up the possibility that optogenetics may be transferred to clinical settings in the near future. Due to clear advantages such as cell-specific stimulation, optogenetics may become a possible alternative to functional electrical simulation (FES) such as DBS and SES,[35] which may eventually replace FES for functional restoration in patients with paralysis following CNS injury.[36] Currently, there are pioneering clinical trials that use optogenetics to restore vision. It is anticipated that clinical trials that restore other neural functions using optogenetics will follow in the near future. Meanwhile, before optogenetics becomes clinically available, optogenetics-inspired electrical stimulation combined with pharmacological intervention may be further developed to circumvent the lack-of-specificity limitation of electrical stimulation.[28]

In addition to invasive neuromodulation methods (DBS, SES, optogenetics, etc.), non-invasive (or minimum-invasive) neuromodulation approaches such as transcutaneous electrical stimulation,[37] transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), focused ultrasound with nanotechnology,[40] pharmacological stimulation and non-invasive DBS[41] have been proved to be effective.[9] For instance, transcutaneous electrical spinal stimulation, a non-invasive neuromodulatory technique, could restore lower urinary track function in 7 patients with spinal cord injury and paralysis.[37] Non-invasive (or minimum-invasive) neuromodulation has the advantage to avoid (minimize or reduce) adverse effects caused by invasive methods (such as bleeding, infection and discomfort), and deserves more research and development.[14] Further research is needed to improve the clinical efficacy and precision of these non-invasive neuromodulation approaches, and integrate them with other neuromodulation techniques or rehabilitation programs to achieve optimal therapeutic effects for functional restoration.

Conclusions

In summary, in recent years, newly developed intervention methods such as spinal cord stimulation (epidural electrical stimulation), optogenetics, BCI and robotics are emerging and flourishing, which has made it possible for precise and effective neuromodulation. With such technical advancements and breakthroughs in neuromodulation, the era of personalized and precise neuromodulation is approaching. In addition to invasive neuromodulation methods, progress has also been made in non-invasive techniques such as transcutaneous electrical stimulation and non-invasive DBS to avoid adverse effects. Multiple modulation approaches can be integrated to reach the full potential of neuromodulation in order to achieve significant clinical effectiveness in functional restoration, reduce adverse effects, and reestablish physiological homeostasis, which may bring cure to patients with incurable symptoms/diseases such as paralysis, AD, PD, ALS and MS, and relieve them from suffering.

Declaration of conflicting interests

The author declares no conflicts of interest.

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